NICEATM

National Toxicology Program Interagency Center for the Evaluation Of Alternative Toxicological Methods

ICCVAM

Interagency Coordinating Committee on the Validation of Alternative Methods

An Overview of ICCVAM and NICEATM

William S. Stokes, D.V.M., D.A.C.L.A.M.
Director
NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

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National Toxicology Program

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DEPARTMENT OF HEALTH & HUMAN SERVICES • USA •

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Outline

- Introduction to ICCVAM and NICEATM
- Scientific Advisory Committee
- Nomination and Submission Process
- ICCVAM Test Method Evaluations
- ECVAM collaborations

What is ICCVAM?

- An interagency committee with designated representatives from 15 federal regulatory and research agencies
- Originally organized by NIEHS in 1994
- ICCVAM Authorization Act of 2000
  - Established ICCVAM as a permanent government committee under the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Methods (NICEATM), located at the NIEHS in Research Triangle Park, NC

What agencies are members of the Interagency Coordinating Committee on the Validation of Alternative Methods ?

Regulatory/Research

- Consumer Product Safety Commission
- Department of Agriculture
- Department of Interior
- Department of Transportation
- Environmental Protection Agency
- Food and Drug Administration
- Occupational Safety and Health Administration

Non-Regulatory/Research

- Agency for Toxic Substances and Disease Registry
- Department of Defense
- Department of Energy
- National Institute for Occupational Safety and Health
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Library of Medicine
- National Institutes of Health, Office of the Director

What is NICEATM ?

- NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (Ni see tum)

- Located at NIEHS, Research Triangle Park, North Carolina
  - 2 government staff; on-site support contract staff

- Functions
  - Administer and provide committee management for ICCVAM; assure compliance with Public Law 106-545
  - Provide operational and scientific support for ICCVAM, Working Groups, Expert Panels
    - Organize test method peer review meetings and workshops
  - Manage validation studies
  - Communicate with stakeholders:
    - http://iccvam.niehs.nih.gov

What are the purposes of ICCVAM[1]?

- *Increase efficiency and effectiveness of Federal agency test method review*
- *Eliminate unnecessary duplicative efforts and share experiences between Federal regulatory agencies*
- *Optimize utilization of scientific expertise outside the Federal government*
- *Ensure that new and revised test methods are validated to meet the needs of Federal agencies*
- *Reduce, refine, or replace the use of animals in testing, where feasible*

[1]P.L. 106-545, ICCVAM Authorization Act of 2002. http://iccvam.niehs.nih.gov/about/PL106545.pdf

What are ICCVAM's Duties[1]?

- *Consider petitions from the public for review and evaluation of validated test methods*
- *Review and evaluate new, revised, and alternative test methods*
  - *submit test recommendations to Federal agencies*
  - *Make agency responses (due within 180 days) available to the public*
- *Facilitate and provide guidance on:*
  - *test method development*
  - *validation criteria and processes*
- *Facilitate:*
  - *acceptance of scientifically valid test methods*
  - *interagency and international harmonization*

[1]P.L. 106-545, ICCVAM Authorization Act of 2000. http://iccvam.niehs.nih.gov/about/PL106545.pdf

Scientific Advisory Committee

- Established by P.L 106-545
- Purpose: *To advise ICCVAM and NICEATM regarding ICCVAM activities*
- *All 15 ICCVAM agency heads, or their designees, serve as non-voting ex officio members (EPA, FDA, CPSC,etc.)*
- Chartered as an NIEHS Advisory Committee
  - Effective January 9, 2002
  - Replaces the Advisory Committee on Alternative Toxicological Methods (ACATM), est. in 1997
  - Designated *Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)*
  - *Also advises NIEHS and NICEATM on NICEATM activities*
  - *Composed of 15 voting members*

Scientific Advisory Committee

- *Required composition (per P.L. 106-545):*
  1. *At least one representative with a history of expertise, development , or evaluation of new, revised or alternative test methods from each of :*
     a. *The personal care, pharmaceutical, industrial chemicals, or agricultural industry*
     b. *Any other industry regulated by an ICCVAM agency*
     c. *A national animal protection organization established under section 501(C)(3) of the Internal Revenue Code of 1986*
  2. *Representatives selected by the Director, NIEHS, from:*
     - *an academic institution*
     - *a State government agency, or*
     - *an international regulatory body, or*
     - *any corporation developing or marketing new or revised or alternative test methodologies, including contract laboratories*

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)

Daniel Acosta, Jr., Ph.D.
Dean, College of Pharmacy
University of Cincinnati

Rodger D. Curren, Ph.D.
President
Institute for In Vitro Sciences, Inc.

Jack H. Dean, Ph.D., Chair
President and Scientific Director, North America
Sanofi-Synthelabo Research Division
Sanofi-Synthelabo, Inc.

Nancy Flournoy, Ph.D.
Professor, Department of Statistics
University of Missouri-Columbia

Alan M. Goldberg, Ph.D.
Director, Center for Alternatives to Animal Testing
Bloomberg School of Public Health
Johns Hopkins University

Sidney Green Jr., Ph.D.
Graduate Professor
Department of Pharmacology
Howard University College of Medicine

A. Wallace Hayes, Ph.D.
Science Advisor
Harvard School of Public Health

Nancy A. Monteiro-Riviere, Ph.D.
Professor, Department of Clinical Sciences
College of Veterinary Medicine
Center for Cutaneous Toxicology
North Carolina State University

Steven H. Safe, Ph.D.
Distinguished Professor
Department of Veterinary Physiology and Pharmacology
College of Veterinary Medicine

Jacqueline H. Smith, Ph.D.
Chesapeake Consulting Team

Carlos Sonnenschein, M.D.
Professor, Department of Anatomy and Cellular Biology
Tufts University School of Medicine

Martin L. Stephens, Ph.D.
Vice President for Animal Research
The Humane Society of the United States

Katherine A. Stitzel, D.V.M.
Independent Consultant

Peter Theran, V.M.D.
Vice President of Health and Hospitals
Director, Center for Laboratory Animal Welfare
Massachusetts Society for the Prevention of Cruelty to Animals

Calvin C. Willhite, Ph.D.
Toxicologist
Department of Toxic Substances Control
State of California

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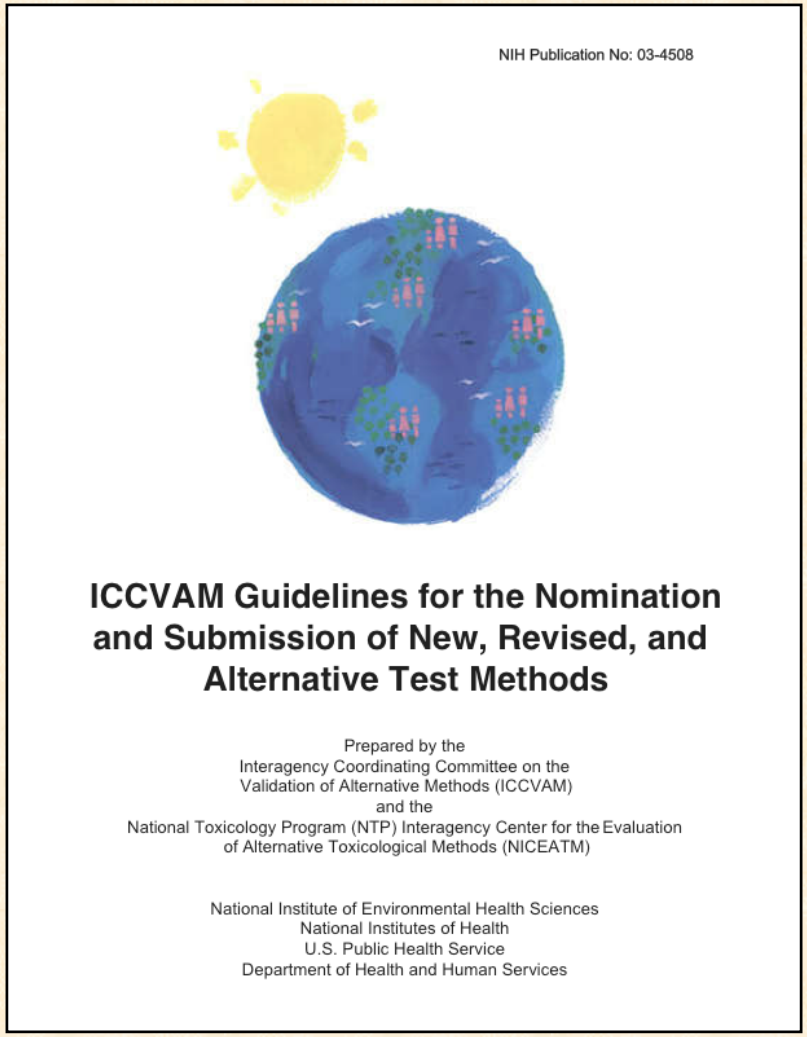
Scientific Advisory Committee on Alternative Toxicological Methods

- Procedures per Federal Advisory Committee Act
  - All meetings open to the public
  - Opportunity for written and oral comments
  - All meetings announced in advance in *Federal Register* notice, ICCVAM and NTP listserves and websites

- Meetings
  - December 5, 2002
  - August 12-13, 2003
  - March 9-10, 2004

- Subcommittees established at August 2003 meeting
  - Strategic planning
  - Priority identification



ICCVAM Guidelines for Test Method Nominations and Submissions[1]

- Updated guidance and process for test method nominations and submissions
  - Data and information needed to assess a test method's current validation status
  - E.g., basis for decisions on standardized protocols and validation study designs
  - Purpose: To facilitate efficient and effective review
- 2003: Addition of Chapter on Performance Standards for Test Methods

[1] ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Toxicological Methods; NIEHS, 2003; http://iccvam.niehs.nih.gov/docs/guidelines/subguide.pdf

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Who can submit methods to ICCVAM for evaluation, and what should be provided?

- Any person or organization can submit test method nominations or submissions to ICCVAM
- Test method submissions should provide information and evidence of scientific validity
  - In accordance with the ICCVAM Test Method Submission Guidelines
  - Submissions are evaluated for completeness, and then prioritized for review
- Nominations for endpoints, issues, or methods that require further evaluation or validation studies can also be submitted for consideration and prioritization
  - No minimum submission requirements, but complete information will expedite consideration

What test methods might be considered by the ICCVAM as "nominations" rather than submissions?

- Test methods proposed for ICCVAM review, but that lack a complete submission package/background review document
- Test methods that appear promising based on limited validation data, and that are proposed for additional validation studies
- Test methods that have been developed, and that are proposed for pre-validation and/or validation studies
- "Nominations" will likely require resources in excess of those necessary for ICCVAM/NICEATM review and evaluation of complete submissions

What criteria are used to prioritize test method submissions and nominations for ICCVAM review and evaluation?

1. The extent to which the proposed method is:
   - Applicable to regulatory testing needs
   - Applicable to multiple agencies/program

2. The extent of expected use or application and impact on human, animal, or ecological health

3. The potential for the method, compared to current methods, to:
   - Refine animal use, i.e., decrease or eliminate pain and distress
   - Reduce animal use
   - Replace animal use

Criteria used to prioritize test method submissions and nominations for ICCVAM review and evaluation:

4. The completeness of the submission with regard to ICCVAM test method submission guidelines

5. The potential for the method to provide improved prediction of an adverse health or environmental effect, compared to current methods

6. The extent to which the test method provides other advantages, such as reduced cost and time to perform, compared to current methods

ICCVAM Test Method Submission, Nomination, and Prioritization Process

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- Solicits, receives, and tracks submissions and nominations from the public and agencies
- Conducts preliminary evaluation report
  - completeness of submissions/nominations
  - preparation of summaries for incomplete nominations
  - recommendations on further evaluation: workshop, expert panel meeting, peer review meeting or validation study

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- Reviews NICEATM preliminary evaluation report
- Recommends draft priority for evaluation or validation study

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SACATM

- Comments on priority of proposals
- Public Comments

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ICCVAM

- Finalizes priority and recommendations
- NICEATM prepares resource requirements

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Director, ETP/NIEHS

- Decisions on resource requests for proposed evaluations and validation studies

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Director, NICEATM

- Informs ICCVAM of test method evaluations/validation studies for which resources are available
- ICCVAM Working Group established
- Test method evaluations or validation studies organized in conjunction with WG

The Revised Up-and-Down Procedure for Acute Toxicity

- **ICCVAM recommendations :**
  - Valid replacement for LD50 for hazard classification
  - Reduces animal use by 60-70%
- **Regulatory acceptance**
  - OECD test guideline: Dec. 2001
  - EPA test guideline: Dec. 2002
  - CPSC, Sept. 2003
  - DOT, July, 2003
- **http://iccvam.niehs.nih.gov**

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In Vitro Methods for Assessing Acute Systemic Toxicity

- ICCVAM International Workshop
- Recommendations for R&D, validation studies:
  - Screening methods
  - Toxicokinetic methods
  - Target organ toxicity methods
  - Chemicals for validation studies
- http://iccvam.niehs.nih.gov

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Guidance Document: Using *In Vitro* Data to Estimate *In Vivo* Starting Doses for Acute Toxicity

- Provides protocols for 2 basal cytotoxicity methods
  - Rodent cell line: 3T3 cells
  - Human cells: NHK
- Supported by ZEBET studies and post-workshop IIVS lab studies
- May reduce animal use an additional 30-40%when used with UDP or ATC
- ICCVAM recommendation: consider using in vitro data to estimate starting doses
- http://iccvam.niehs.nih.gov

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Alternative Tests for Acute Oral Toxicity

Test Method	No. of Animals	No. of Deaths	Time to Conduct (in-life)
Original TG 401 (1981)	~ 45	Up to 25	14 days + s.s.[1]
Revised TG 401 (1987)	~ 25	Up to 12	14 days + s.s.[1]
Revised UDP: TG 425 (2001)	6 - 9	0-6[2]	6-30 days[3]
Revised UDP + *in vitro* test	3 - 6	0-3[2]	3-24 days[3]

[1]S.S.: Sighting study for dose-range finding

[2]When appropriate for use; no deaths may occur for nontoxic substances; all animals may die for highly toxic substances.

[3]Shortest duration is for highly toxic substances (LD50 ≤ 5 mg/kg - Category 1); longest duration would result for chemicals with intermediate to no toxicity (Categories 2-5: 5 ≤LD50 >5000 mg/kg).

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What other test methods have been evaluated by ICCVAM ?

- In Vitro methods for skin corrosivity (4)
- Murine Local Lymph Node Assay (LLNA)
  - Eliminates pain and distress; fewer animals; shorter time
  - Accepted by FDA, EPA, CPSC, OSHA; OECD TG 429
- Frog Embryo Teratogenesis Assay: FETAX
  - Recommendations provided to improve reproducibility and accuracy of the assay
- *In vitro* estrogen and androgen receptor assays (4)
  - No adequately validated test methods
  - ICCVAM recommendations for:
    - Minimum procedural standards (essential test method components) that should be incorporated into standardized protocols
    - Reference chemicals for validation studies
    - Priority test methods for development and validation
      Emphasis on non-animal sources of receptor

ICCVAM-NICEATM Collaborations with the European Center for the Evaluation of Alternative Methods (ECVAM)

- International guidance on application of GLPs to *in vitro* toxicity testing
  - March, 2003: Joint presentation to the OECD GLP Working Group
  - September, 2003: GLP WG decision to develop an international guidance

- Joint planning for *in vitro* dermal irritation validation study
  - ICCVAM and NICEATM participation on SMT; reference chemical contributions

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ICCVAM-NICEATM Collaborations with ECVAM - 2

- Reciprocal observer status at ESAC/SACATM meetings
- Joint international validation study on *in vitro* methods for acute toxicity
  - Phase III completion: June 2004
- Joint participation in upcoming workshops:
  - Acute systemic toxicity (9-03)
  - Validation of toxicogenomic-based methods (12-03)
  - Good cell culture practices (2004)

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ICCVAM Agency Representatives*

ATSDR	William Cibulas Moiz Mumtaz
CPSC	Marilyn Wind (Vice-chair) Susan Aitken Kailash Gupta Patricia Bittner
USDA	Jodie Kulpa-Eddy Elizabeth Goldentyer
DOD	Robert E. Foster Patty Decot Harry Salem John Frazier
DOE	Marvin Frazier Marvin Stodolsky
DOI	Barnett Rattner Sarah Gerould
DOT	George Cushmac Steve Hwang
EPA	Richard Hill, OPPTS Angela Auletta, OPPT Karen Hamernik, OPP Harold Zenick, ORD Suzanne McMaster, ORD Maurice Zeeman, OPPT
FDA	Leonard Schechtman, NCTR (Chair) Suzanne Fitzpatrick, ORA Abigail Jacobs, CDER Raju Kammula, CDRH Melvin Stratmeyer, CDRH Richard McFarland, CBER David Hattan, CFSAN Robert Bronaugh, CFSAN Devaraya Jagannath, CVM William Allaben, NCTR Martha Moore, NCTR Atin Datta, ORA
NCI	David Longfellow Alan Poland
NIEHS	William Stokes John Bucher Rajendra Chhabra Jerrold Heindel
NIOSH	Paul Nicolaysen Douglas Sharpnack
NIH	Margaret Snyder Nelson Garnett
NLM	Vera Hudson Jeanne Goshorn
OSHA	Surrender Ahir

* August 2003

NICEATM Staff

NIEHS

William S. Stokes, D.V.M.	Director; Project Officer
Debbie McCarley	Special Assistant; Asst. Project Officer

Center Support Contract (ILS, Inc.)

Raymond Tice, Ph.D.	Principal Investigator (half-time)
Bradley Blackard, M.S.P.H.	Project Manager
Sue Brenzel	Webmaster
Neepa Choksi, Ph.D.	Toxicologist
Christina Inhof, M.S.P.H.	Sr. Project Coordinator
Linda Litchfield	Administrative Assistant/Mtg. Planner
Judy Strickland[1], Ph.D.	Sr. Toxicologist
Michael Paris[1]	Sr. Project Coordinator

[1]Contract Option Staffing (Validation Study Coordination)